PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies.
AUTHORS	Pijls, Bart; Jolani, Shahab; Atherley, Anique; Derckx, Raissa; Dijkstra, Janna; Franssen, Gregor; Hendriks, Stevie; Richters, Anke; Venemans-Jellema, Annemarie; Zalpuri, Saurabh; Zeegers, Maurice

VERSION 1 – REVIEW

REVIEWER	Nicholas Jones University of Oxford, UK
REVIEW RETURNED	21-Sep-2020

GENERAL COMMENTS	Thank you for the opportunity to review this systematic review and meta-analysis of demographic risk factors related to COVID-19. I appreciate the authors have followed systematic review guidance and the methods are clearly stated and justified. Major comments: 1. Much has been published in this field already, including large database analyses of risk factors for contracting COVID and also COVID-related mortality (e.g. OpenSafely and others) that have demonstrated an association between age and sex with risk of COVID and more severe outcomes. Some of these are large studies, including several thousand patients with COVID, with adjustments made for possible confounders in regression analysis. How do the authors feel this review extends knowledge in relation to COVID risk factors beyond the association that has already been shown in these individual studies? 2. As the authors highlight, research in COVID is evolving rapidly and yet the most recent included study in this paper is now over 5 months old (mid April). The review draws heavily on early papers from China and has not captured many subsequent international papers looking at COVID epidemiology. I wonder whether a search update is necessary before this is published if the review is to provide up to date results? Similarly, the search is limited to two databases - I wonder if searches in MedRxiv and LitCovid were considered to help identify new and emerging evidence that would ensure this review is up to date? 3. Increasing age will be associated with increasing prevalence of co-morbid disease, which will also increase risk of COVID severity and death e.g. chronic kidney disease and hypertension. Similarly there are differing risks of other co-morbid disease between sexes

	that are likely to be relevant. I think when pooling different studies it would be important to provide information on which potential confounders were accounted for in the original studies and how this impacts on the original and pooled results. It is not clear at present whether the pooled RR being reported are based on adjusted or unadjusted original results and if unadjusted this is a key limitation. Pages 58 to 64 and pages 77 to 83 are blank on the version I can access but I dont see any information outlining characteristics of the populations, case ascertainment or study setting (ie. primary v secondary care) within the original studies. Minor It would be helpful to know more details or duration of follow-up across studies. I also suggest making it clearer in the text the number of studies included in each individual meta-analysis. A subgroup analysis was planned on study setting and diagnostic modality - were these performed?

REVIEWER	Fenicia Vescio Istituto Superiore di Sanità, Italy
REVIEW RETURNED	30-Sep-2020

GENERAL COMMENTS	the article is interesting, well written and methodologically sound. I have no specific comments to make.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment 1
Thank you for the opportunity to review this systematic review and meta-analysis of demographic risk factors related to COVID-19.

I appreciate the authors have followed systematic review guidance and the methods are clearly stated and justified.

Response: Thank you for your positive feedback and thorough evaluation of our paper.

Comment 2
Much has been published in this field already, including large database analyses of risk factors for contracting COVID and also COVID-related mortality (e.g. OpenSafely and others) that have demonstrated an association between age and sex with risk of COVID and more severe outcomes. Some of these are large studies, including several thousand patients with COVID, with adjustments made for possible confounders in regression analysis. How do the authors feel this review extends knowledge in relation to COVID risk factors beyond the association that has already been shown in these individual studies?

Response: Thank you for this comment. Indeed, the pooled estimate of our paper compares well with the estimates found in e.g. the OpenSafely study: for COVID-19 related mortality OpenSafely reports a HZ of 1.78 for gender indicating higher risk of death for males. This HR of 1.78 is very similar to our

pooled relative risk of 1.5 (95%CI 1.18 to 1.91). However, most studies are based on data from a single country often at a single point in time. This study combines results of multiple studies being able to compare within the same country and across different countries. Consistency of outcomes in heterogenous populations helps us to understand the real distribution of COVID across the different demographic factors. As the purpose of this study is to reveal the real-life patterns, we believe that the effect estimated should not be adjusted for sex and age (as most large studies using single country pooled data do). Please also see comment 4 from reviewer 1 In addition, this review has added a quality assessment of the individual studies.

Comment 3
As the authors highlight, research in COVID is evolving rapidly and yet the most recent included study in this paper is now over 5 months old (mid April). The review draws heavily on early papers from China and has not captured many subsequent international papers looking at COVID epidemiology. I wonder whether a search update is necessary before this is published if the review is to provide up to date results? Similarly, the search is limited to two databases - I wonder if searches in MedRxiv and LitCovid were considered to help identify new and emerging evidence that would ensure this review is up to date?

Response. This review focussed on peer-reviewed papers during the early phase in the pandemic. We had therefore decided on a closing date. Besides, an update of the literature search revealed more than 40.000 new hits for the screening phase, which has become an unrealistic workload for adding to this review. Having said that, there were no apparent differences between the China and non-China studies as can be seen in the forest plots (Figures 2 through 9).

The following was added to the methods:

“For this review we focused on the early phase in the pandemic.”

Comment 4
Increasing age will be associated with increasing prevalence of co-morbid disease, which will also increase risk of COVID severity and death e.g. chronic kidney disease and hypertension. Similarly there are differing risks of other co-morbid disease between sexes that are likely to be relevant. I think when pooling different studies it would be important to provide information on which potential confounders were accounted for in the original studies and how this impacts on the original and pooled results. It is not clear at present whether the pooled RR being reported are based on adjusted or unadjusted original results and if unadjusted this is a key limitation.

Response: This study reported unadjusted risk ratios for the demographic factors age and sex for several COVID-outcomes. Some studies have indeed reported adjusted risk ratios, but these adjustments were often made for the investigation of different research questions. Since a lot is to be determined about the causal path of infection, hospitalization and death related to COVID, adjusted analyses are not yet warranted. At this stage, we feel like it is more important and more appropriate to describe patterns of COVID outcomes across the determinant subgroups, i.e. without adjustment for haphazardly selected confounders that could actually introduce bias. To make sure it is clearly conveyed that our estimates are unadjusted, we have specified the way we have extracted data from the source papers.

Comment 5
Pages 58 to 64 and pages 77 to 83 are blank on the version I can access but I dont see any information outlining characteristics of the populations, case ascertainment or study setting (ie.

primary v secondary care) within the original studies. [Note from Editor - the inclusion of spreadsheets as supplemental files has caused many blank columns to fill pages - please transfer the relevant information to tables in Word]

Response: Our apologies for this inconvenience. This appendix table is now uploaded as a word file.

Comment 6
It would be helpful to know more details or duration of follow-up across studies.

Response: The range of follow-up was added to the results:

“The follow-up ranged from 12 days to 73 days.”
Details on individual study basis are reported in the Appendix II.

Comment 7
I also suggest making it clearer in the text the number of studies included in each individual meta-analysis.

Response: The number of studies for each meta-analysis have been added to the text.

Comment 8
A subgroup analysis was planned on study setting and diagnostic modality - were these performed?

Response: These subgroup analyses were not performed because there was too little variation in study setting and diagnostic modality, for each meta-analysis, to allow for a meaningful analysis. The following lines were added to the methods:

“The study setting and diagnostic modality were very consistent within the different outcomes, so a sensitivity on these factors was not meaningful.”

Reviewer 2
Comment 1
the article is interesting, well written and methodologically sound. I have no specific comments to make.

Response: Thank you for this positive evaluation and your interest in our paper.